Hyperlipidemia: Case Studies as Evidence for Optimal Treatment

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Objectives

- Summarize the key evidence from recent large lipid treatment trials.
- Explain and apply the NCEP/ATP III guidelines to patients.
- Discuss the risks and benefits of various treatment options and the evidence supporting these options for use in patients.
- Have fun with real cases!!

Why Bother?

- Optimum treatment of lipids helps in the primary & secondary prevention of ASCVD; still our nation's #1 killer
- We have a long way to go…
  - RAND; 1st National Report Card on Quality of Care; NEJM 26 June 2003
  - Only 48.6% of patients are receiving recommended care for hyperlipidemia

NCEP/ATP III – 15 May 2001

- **www.nhlbi.nih.gov**
- **LDL remained the main treatment goal, but LDL goals lowered**
- **Raised acceptable HDL to 40**
- **Lowered TG goal to 150**
- **Risk Factor assessment enhanced with the 10-yr Framingham risk calculator**
- **Added the Metabolic Syndrome to Tx**

NCEP/ATP III – 9 Steps

- Step 1: Obtain, complete & fasting lipids.
- Interpret: LDL < 100 optimal
  LDL 100-129 near optimal
  LDL 130-159 borderline high
  LDL 160-189 high
  LDL >190 very high

NCEP/ATP III

- Step 2: Identify if patient has CAD or equivalent (PAD, DM, AAA, Carotid)
- Step 3: Risk factor assessment (HTN, FHx, Tob, Age & Sex, HDL<40 or >60)
- Step 4: If 2 or more risk factors; do Framingham 10-yr risk assessment.

NCEP/ATP III – Step 5

Risk Category	**LDL Goal**	**Start T.L.C.**	**Start Drug Treatment**
CHD/10yr risk>20%	<100mg/dl	>100mg/dl	>100 – 129mg/dl
2+RF or 10yr<20%	<130mg/dl	>130mg/dl	>130 – 160mg/dl
0-1 risk	<160mg/	>160mg/	>160

NCEP/ATP III – Step 6

- Initiate Therapeutic Lifestyle Changes (TLC)
  - AHA Step 2 diet
  - Soluble fiber 10-25gm/day
  - Plant sterols/Sitostanol (Benecol®, Take Control® margarines) - lower LDL 10%
  - Increased exercise
  - Weight management

NCEP/ATP III – Step 7

- Add drug therapy simultaneously to TLC in patients with CHD or equivalent. Add drugs after 3 months if TLC not effective in other risk categories.

- Best unbiased source for review of drug treatment: “The Medical Letter: Choice of lipid regulating drugs” 43:2001,pp43-48. 2003 update

Drugs – Step 7 (cont.)

- **Resins**- (cholestyramine,colestid, colesevelam): lower LDL; adjunct to statins; GI side effects/malabsorption issues
- **Niacin-** “miracle agent”, cheap & moves every parameter in the right direction. But, side effects problematic. Need slow dose titration and pre-med with ASA. Caution with Diabetes; can worsen glycemic control

  Most potent increase of HDL.

Drugs – Step 7 (cont)

- **Fibrates** – (fenofibrate, gemfibrozil) lower TG and raise HDL. Can combine with statins but caution re: hepatic side effects. Cutting statin dose by ½ is good rule.
- Keep simvastatin dose no greater than 10mg if combined with a fibrate or >1000mg of niacin.

Newer Drugs – Step 7 (cont.)

- **Ezetimibe (Zetia®)-** new class that inhibits the intestinal absorption of cholesterol. Lowers LDL 17%, TG 6%, increases HDL by 1.3%. Combined with a statin increases effects of statin by 10-15% w/o side effects. VERY well tolerated at 10mg/d.
- VYTORIN® - ezetimibe + simvastatin

Newer Drugs – Step 7 (cont)

- **<u>Lovastatin + Niacin (Advicor®)-</u>** in fixed combos 20/500, 20/750, 20/1000. Increase dose *monthly* up to max 40/2000. Max dose w/ LDL decrease 45%, TG 42%, and HDL increase by 41%. Causes less flushing and hepatic effects than any niacin formulation. Greater risk of myopathy than a statin alone.

Drugs – Step 7 (cont.)

- **<u>Statins-</u>** All w/ anti-inflammatory effects. None safe in pregnancy. All are more potent by 10-15% with evening dosing.

  - muscle pain = 1-5%

  - hepatitis (transaminases>3x nl.) = 0.5%

  - rhabdomyolysis = rare; incidence *rates per million Rx's*: pravastatin0.04, lovastatin0.19 atorvastatin 0.04, simvastatin 0.12.

  (*cerivistatin was 16-80x these rates!!)*

Drugs – Step 7 (cont.)

- Atorvastatin – greatest LDL lowering w/ good TG lowering
- Lovastatin: take w/ food; generic version
- Pravastatin: least drug interactions due to different elimination pathway; take on empty stomach
- Simvastatin: #2 in potency; lots of data
- Fluvastatin: less potent; poor prevention data
- Rosuvastatin: new release; very potent; 5 - 40 mg (CRESTOR®); may raise HDL a bit more & lower TG. Caution w/ CrCl<30cc/min and ??? in Asians.

Statin Pearls

- Elevated transaminases on statins; (unless reaching 3x normal), are not a reason to stop the statin – they are are a reason to watch closely.
- Statin side effects are often agent specific, not always class specific.
- Unexplained myalgias may occur on statins without CK elevation. Try a different statin.

Statin Pearls

- Rhabdomyolysis is uncommon unless CK is elevated to 10 x normal.
- Unless you enjoy driving yourself nuts; do not check CK serially in patients on statins. Remember vigorous yard work will bump your CK!

PROVE-IT Trial

- Designed to “PROVE” that 80mg atorvastatin was no better than 40 mg pravastatin in secondary prevention.
- But, atorvastatin was superior *as early as 30 days of therapy*. In just 24 mths the atorvastatin group (meanLDL=62) had 16% less of all CV events. 28% less mortality than pravastatin group (meanLDL=95)

Updated ATP-III Guidelines

RISK	LDL	TLC	DRUGS
HIGH >20% 10yr	**<70mg/dl Optional**	**>100mg/dl**	**>100mg/dl or <100mg**
Mod. High 10-20%	**<100mg/dl Optional**	**>130mg/dl**	**>130mg/dl or 100-130**
Moderate <10% 10yr	<130mg/dl	>130mg/dl	>160mg/dl
LOW	<160mg/dl	>160mg/dl	>190mg/dl

NCEP/ATP III – Step 8

- Identify Metabolic Syndrome: (3 of 5)
  - SBP>130, FBS>110, TG>150, HDL<40 in men and <50 in women, waist>40”men, 35”women

Aggressively:

- Treat underlying causes of overweight and physical inactivity.
- Treat HTN, use ASA for CHD patients

NCEP/ATP III – Step 9

- Treat elevated TG (>150mg/dl)
  - First lower LDL; if TG still >200 consider adding/increasing drug therapy
  - But, if TG >500mg/dl, first lower triglycerides to prevent pancreatitis. When they are <500 then return to LDL lowering
  - Treat HDL <40 after lowering LDL.

CASES

- All real cases. No “perfect answers”.
- All present real Family Practice dilemmas.
- Will use the evidence to help formulate a “best” answer.
- Use cases t g edge info.

Case #1- The Well Elderly

- 82 yr old woman with no significant medical history who checked her cholesterol at a health fair and was told she needed to see her family doctor because it was high.
- Your recheck:
- TC=254 LDL=188 HDL=41 TG=125

Case #1

- PMHx: osteoarthritis and systolic HTN
- Meds: celecoxib 100mg qd, HCTZ 25mg qd
- FHx: 3 relatives who have lived to >100yrs
- PE: 66” 138lbs P=70 BP=158/77
  - Rest of exam non-contributory

  - WHAT DO YOU DO?

Case #1

- Apply NCEP: risk assessment? 2 RF so Framingham Risk = 27% 10yr risk
- Check Step 5?

- If we choose a med, best med to lower her LDL is a statin.
- But, should we prescribe a med?

Case # 1

- Things to consider:
- Statin trials excluded folks >65 yrs
- But, NNT at this age is 4:1 vs. 35:1 for a middle aged man.
- Side effects? Drug interactions? Cost?
- PROSPER

Case # 1

- PROSPER; Lancet 2002:360; pp1623-30.
- Used 40mg/d of pravastatin in patients 70-82 yrs of age (majority women) in both primary **and** secondary prevention.
- 24% Rel Risk Red (RRR) of CHD death, 25% RRR in TIA, in just 3 years of use.
- Drugs tolerated extremely well-even w/ multi-Rx.
- “Long-term statin therapy should be considered routinely largely irrespective of age”

Case # 1

- Maycock CA et al; JACC 2002;40:1777-85.
- Statin tx in patients >80yrs. Mortality rate was **8.5%** in those on statins **vs. 29.5%** in those not taking statins.

- So you could consider an RX Statin for this elderly woman; certainly need to optimize her HTN control as first priority.

Case #2 – Diabetes

- 55 year old male with Type II Diabetes and HTN for 5 years. He has refused treatment for elevated cholesterol in the past – but is willing to discuss it now.
- Other PMHx: GERD, Irritable Bowel
- Meds: Metformin, lisinopril, omeprazole, metamucil
- FHx: DM, MI in F at 58, PGF at 60

Case #2 - Diabetes

- TSH: normal
- TC = 235 HDL = 28 TG = 185 LDL =170
- PE: 69” 268lbs P=74 BP = 136/82
- An obese male who seems to be mildly short of breath just moving around the exam room.

Case #2 - Diabetes

- Risk Assessment: EASY ! DM=CHD
- Want LDL < 100. Perhaps <70
- Begin TLC; also consider the simultaneous start of ASA and a statin.
- Evidence: MRC/BHF Heart protection study of cholesterol lowering in 20,536 high risk individuals. Lancet. 2002; 360: 7-22.

Case #2 - Diabetes

- This large study showed that treatment with simvastatin; *regardless of its numerical effect on lipid values* helped to reduce all endpoints (MI, CVA, revascularization). This was especially true for those with Diabetes.

Case #2 - Diabetes

- Start simvastatin 20 mg po qd and check LFT at 6weeks. (normal) Check LFT and lipids at 12 weeks. LFT nl but;
- TC = 198 HDL = 30 TG = 180 LDL = 132
- You increase simvastatin to 40 mg and recheck in 12 weeks;
- TC = 178 HDL = 31 TG = 174 LDL = 112

Case # 2 - Diabetes

- What next?
- Optimize your Diabetes control
- Optimize your dietary and exercise plan
- Consider adding a fibrate
- Consider a change to Advicor®
- Don’t ignore the low HDL/high TG – see Step 8/9 of the NCEP/ATP III

Case # 3 – “Middle-of the Road”

- 45 year old woman who on a routine lipid screen has the following values:
- TC = 203 HDL=48 TG = 155 LDL = 124
- PMHx: negative, smoker
- Meds: daily vitamin
- FHx: MI in F age 60, M age 64
- PE: 65” 130lbs P=72 BP=118/68

Case #3 – “Middle of the Road”

- Risk Factors: 2 ; Framingham = 5% risk
- NCEP/ATP III says that she is at her LDL goal; e.g. <130
- But, concerns remain: FHx, Smoking, HDL is <50 & TG >150; both less than ideal.
- What do you do with this “middle-of-the-road” risk profile?

Case# 3 – Middle of the Road

- Consider a new idea: measure her hs-CRP
- Facts: CRP is a marker of inflammation.
- ASCVD is a disease of inflammation
- Multiple prospective epidemiological (vs. interventional studies) have shown that CRP can predict MI,CVA, PAD, sudden cardiac death.

Case #3 – Middle of the Road

- Hs-CRP assays are now widely available; can check non-fasting, anytime of day.
- < 1mg/l = low risk
- 1-3mg/l = moderate risk
- >3mg/l = high risk
- **>10mg/l = invalid for cardiac risk prediction;consider 1° inflammatory disease, trauma, serious infection.**

Case # 3 – Middle of the Road

- CRP predicts risk *independently* of age, smoking, LDL, HDL, BP, Diabetes, sex.
- CRP has long-term predictive value
- CRP is a stronger predictor of risk than LDL
- CRP does not supplant other risk factor assessment – it is a powerful adjunct!

Case #3– Middle of the Road

- PRINCE (PRavastatin INflammation/Crp Evaluation trial; JAMA 2001:286;64-70. And other trials have proven that Statins lower CRP 15-25% within 6 weeks of initiation.
- Weight loss, exercise and smoking cessation also lower CRP.

Case # 3 – Middle of the Road

- CARE & AFCAPS/TEXCAPS both suggest that the benefit of statin therapy among those with *low LDL but high CRP may be as large as those with overt hyperlipidemia.*
- How to answer this ?
- 2003: 15,000 patients with native LDL<130 but CRP above 2.0mg/l. All will be put on a statin for prevention. What will happen?

Case # 3– Middle of the Road

- What does this mean for our patient?
- CRP is most useful in those judged at intermediate risk and in primary prevention.
- Review; 45 yr old woman with an LDL<130 but +FHX and other borderline risks…eg a 5% Framingham risk
- HOW about checking an hs-CRP to further assess her risk ?

Case # 3 – Middle of the Road

- CRP = 3.2mg/l HIGH risk
- Studies have proven she is in fact at risk; more than her LDL would tell us. What to do?
- Smoking cessation will lower CRP
- Statins will lower her CRP
- But, no prospective proof that this will change her outcome.

Case # 4– The Unreachable Goal

- 60 yr old male returns to see you 3 months after a 4vCABG. He feels great. At his last visit with his CT surgeon he was told; “follow-up with your family doctor to get your cholesterol in control”
- PMHX: HTN x 20 yrs, BPH, ED, mild OA
- MEDS: ASA, Metoprolol 50 mg po bid, Viagra®,

  Simvastatin 20 mg po qd
- FHX: F with CVA at 68

Case # 4 – The Unreachable Goal

- PE: 70” 160lbs P=60 BP=124/76
- Cor: RRR, no m/r/g, no jvd, healed median sternotomy scar
- Ext: no edema
  Lungs: slight dec. breath sounds
- TC=180, HDL=42 TG=100 LDL=118

Case # 4 – The Unreachable Goal

- Risk Assessment = he has CHD; 2° prev.
- Goal LDL is <100 or < 70 per NCEP
- At <100 atherogenesis seems to arrest
- At an LDL of < 80 in mammalian species atherogenesis reverses. Also the PROVE-IT trial shows that an LDL of 62 was superior to an LDL of 95.

Case #4 – The Unreachable Goal

- You decide to increase the simvastatin to 40mg po qd.
- 6 weeks later; TC= 170 TG=105 HDL=42 LDL=107
- What do you do?

Case # 4– The Unreachable Goal

- Many options: 1)increase simvastatin to 80 mg or change to atorvastatin or rosuvastatin.
- PROBLEM: inc risk of side effects and less LDL lowering effect as you inc statin doses. For every doubling of dose, LDL decreases by only 6 %. A threefold higher dose by 12% and a fourfold increase lowers LDL cholesterol by only 18%.

Case # 4– The Unreachable Goal

- 2.) Add Ezetimibe 10 mg po qd: less chance of side effects; should help to reach goal LDL easily.
- 3.) Intensify diet; Ornish Plan; add soluble fiber, add soy, add omega-3 fatty acids.
- 4.) Be satisfied and await more trials…

Summary

- **7 Points to make you**
- 1) Primary & Seconda
  Prevention of ASCVD a
  possible!
  2) NCEP/ATP III at

www.nhlbi.nih.gov is a wonderful tool.

Summary – 7 Points

- 3) Better medication options are a help: Ezetimibe, Advicor®, new statins and a cleaner understanding of statin side effects
- 4)Attack the metabolic syndrome!! A multi-modal treatment plan is best.
- 5) Don’t ignore a chance for prevention because your patient is >70 or <35.

Summary – 7 Points

- 6) hs-CRP is a powerful new tool to predict risk; especially in those at intermediate risk.

  But, we need prospective proof that lowering it will help reduce ASCVD endpoints.

  7) Try to get to goal; How low should we go? Await new trials & anticipate new ATP-IV guidelines.

Thanks for your Attention!